MILLENNIUM

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3 August 2005

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Re: Draft Guidance for Industry: Safety Testing of Drug Metabolites.
[Docket No. 2005D-0203, 70 *Federal Register*, 32839, June 6, 2005]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. ("Millennium"), a leading biopharmaceutical company based in Cambridge, Mass., markets VELCADE® (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in two disease areas, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium welcomes FDA's publication of draft guidance on safety testing of drug metabolites and we wish to comment as follows.

As a general remark, we believe that the pharmaceutical industry has understood, for many years, the importance of safety testing metabolites of new therapeutics[1] including, but not limited to, human-unique metabolites or those poorly represented (by the area under the curve (AUC)) in the non-clinical toxicology species. However, in an effort to derive a threshold level with which one would conceivably initiate metabolite safety testing, the draft Guidance has relied on examples that would actually have been shown to be toxic in non-clinical toxicology testing. In fact, most of these examples

[1] *Toxicol. and Appl. Pharmacol.* (2002), **182**, 188-196.

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would not have been affected by the proposed testing paradigm (Appendix A). Historically, most of the compounds tested in non-clinical and clinical safety assessments would fall into the category given in this Guidance as "no testing required", i.e. metabolite exposure in non-clinical species is equal to, or greater than, human exposure (Appendix A, box **A**). Consequently, the standard safety assessment of the parent compound would suffice (Appendix A, box **D**). While it is recognized that the formation of metabolites unique to humans is uncommon (see Guidance, lines 169-170), such an occurrence would lead a sponsor to design a suitable safety assessment and gain FDA's agreement to it before commencing tests. Therefore, we believe that the Guidance addresses only the most common situation when metabolite exposure in the non-clinical species is equal to, or greater than, that in the human (Appendix A, box **A**).

Given the infrequency of the inverse situation (Appendix A, box **B**), and the even greater rarity of a metabolite being unique to humans (Appendix A, box **C**), we recommend that the Guidance provide for case-by-case assessments in consultation with FDA for such occurrences, rather than the blanket 10% threshold defined in this draft. Additionally, the proposed lower percentage (10%) at which the safety assessment of a metabolite would be initiated would result in the implementation of practices that would increase animal usage during toxicity assessments, and thereby substantially increase the cost of drug development, both of which run contrary to FDA's critical path initiative[2]. We believe that a more sensitive and specific approach would be more efficient for all.

Our proposed process would permit the best possible decision to be made based on all the available data from the sponsor, the evolving literature and FDA safety database on related compounds, and the unique needs of the patient population. Such a decision to proceed with metabolite testing should also reflect a risk-benefit consideration, e.g., oncology therapeutics.

SPECIFIC COMMENTS

We have several specific concerns as follows:

1) The Need for Testing
   a) Lines 26-30; lines 71-73 - As mentioned in our comment above, the 10% threshold was derived from the consideration of a select subset of drugs known to produce reactive metabolites or that are themselves pro-drugs.
   b) Lines 180-182 - We believe that there is a misconception that one can assume systemic exposure to a metabolite or its conjugates if they are observed in the excreta; this is not necessarily the case and systemic exposure to metabolites should only be considered on the basis of specific evidence (with minor exceptions).

[2] *Challenge and Opportunity on the Critical Path to New Medical Products*. US Dept. of Health and Human Services, Food and Drug Administration. March 2004.

c) Line 208 - The issue of drug impurities is mentioned vaguely. Drug impurities are independently assayed for potential toxicity and, therefore, in our view are not within the scope of this Guidance.

2) Therapeutic Indications
   a) It is not clear whether oncology therapeutics, which are often considered to have different risk:benefit profiles from other drugs, are subject to the recommendations of the present guidance. We would request that this be clarified.

3) Timing of Nonclinical and Human ADME Studies
   a) Lines 62 – 65, lines 282 – 286 - The Guidance repeatedly and unreservedly promotes the early conduct of human metabolic (ADME[3]) studies using radiolabeled drug. While we recognize that there are circumstances when the early availability of these data is helpful, the studies are complicated and expensive to run and, historically, have been performed even in late Phase 2 without any negative impact upon the sponsor's ability to plan the development of the drug. We suggest that the recommendations to perform these studies early should be expressed in more qualified and nuanced terms.

4) Safety Testing of Metabolites: Study Type and Dosing.
   a) Lines 182-184 state *"We recommend consulting the ICH Q3A guidance with regard to the development of analytical methods for measuring metabolites in selected matrices."* The guideline quoted is *"Impurities in New Drug Substances"*, which does not seem to be appropriate. What was perhaps meant to be cited was ICH S3A, *"Note for Guidance on Toxicokinetics"*. The Guidance should have perhaps cited the FDA's own guidance *"Guidance for Industry: Bioanalytical Method Validation"*, issued in 2001.
   b) Lines 235-237 - The concept of testing metabolites in non-clinical toxicology species to identify the maximum tolerated dose (MTD) is not scientifically justified. While it is important to identify the toxicity of some of the metabolites, it would be more clinically relevant to test the metabolite(s) at an exposure multiple to that of humans, i.e. 3X, 10X, etc.
   c) Lines 249-251 - The guidance states that two independent genetic toxicity tests should be used, a bacterial reverse mutation and an *in vitro* clastogenicity assay. We propose that it should be acceptable, as an alternative, to use the mouse lymphoma assay with both colony counting (mutagenicity) and colony sizing (clastogenicity) as a suitable genetic toxicity test, since it is well recognized that this single test yields equivalent information and is, therefore, more efficient.
   d) Lines 242-244 - The guidance states that safety pharmacology, in particular QTc prolongation, should be studied for some metabolites. This testing would not occur until after Phase I testing in either normal healthy volunteers or patients. During the Phase I testing, the QTc interval can typically be assessed. If there is no signal of QTc prolongation from the Phase I testing, then there should be no concern for *torsades de pointes*, and a dog QTc study is not warranted, as this

[3] Absorption, Distribution, Metabolism, Excretion.

would be using animals in testing that will not add to our knowledge of the safety of the compound in question.

e) Lines 193-196 - It is stated several times throughout the guidance that computational toxicology be used to predict potential toxicity, be it either genotoxicity or reproductive toxicity. It is widely accepted that there are several proprietary software programs that can predict genotoxicity with some concordance (e.g., MultiCASE™ and DEREK™ for Windows). However, there is not an acceptable "off the shelf" software program that can predict reproductive toxicity, so references to predicting reproductive toxicity should be removed from the Guidance.

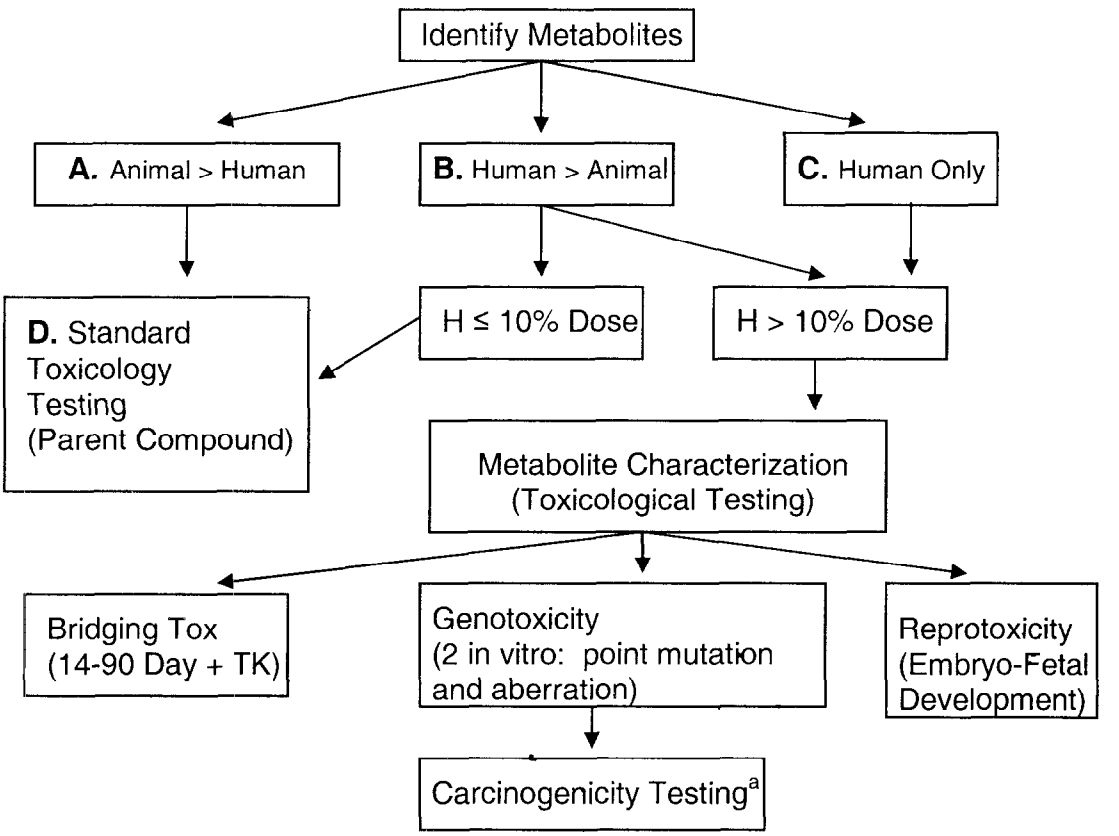
We appreciate the opportunity to comment on this important guidance and look forward to working with FDA to realize its potential.

Sincerely,

Robert G. Pietrusko, Pharm.D.,
Senior Vice-President, Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc

APPENDIX A: DECISION TREE FLOW DIAGRAM

(modified from Guidance for Industry/Safety Testing of Drug Metabolites)



[a] Carcinogenicity testing may be needed on a case-by-case basis, independent of the results of genotoxicity testing (see Section IV.D).